

EXHIBIT A

Mesothelioma Associated With the Use of Cosmetic Talc

Jacqueline Moline, MD, MSc, Kristin Bevilacqua, MPH, Maya Alexandri, JD, and Ronald E. Gordon, PhD

Objective: To describe 33 cases of malignant mesothelioma among individuals with no known asbestos exposure other than cosmetic talcum powder. **Methods:** Cases were referred for medico-legal evaluation, and tissue digestions were performed in some cases. Tissue digestion for the six cases described was done according to standard methodology. **Results:** Asbestos of the type found in talcum powder was found in all six cases evaluated. Talcum powder usage was the only source of asbestos for all 33 cases. **Conclusions:** Exposure to asbestos-contaminated talcum powders can cause mesothelioma. Clinicians should elicit a history of talcum powder usage in all patients presenting with mesothelioma.

BACKGROUND

Asbestos in all forms is recognized by the International Agency for Research on Cancer (IARC) as a human carcinogen and all forms of asbestos are recognized as the primary risk factor for malignant mesothelioma.^{1–5} By the mid-1950s, over 60 cases of asbestos-related lung cancer had been published in the literature. In 1955, Doll¹⁰ published a seminal paper describing the increased risk of lung cancer among asbestos-exposed workers. In 1960, Wagner et al² published a study of 33 cases of malignant mesothelioma among individuals who were exposed to asbestos in and around the crocidolite mines in South Africa. By the mid-20th century, as asbestos use rose in the industrialized world, diseases associated with its use also began their upward curve.^{3,8,11,12} On average between 2003 and 2008 1.05 cases per 100,000 of malignant mesothelioma (MM) were diagnosed in the United States and in 2015, 2597 deaths resulted from the disease.^{13,14}

The presence of asbestos in talc and talcum powder consumer products including body powder, baby powder, facial cosmetics, and pharmaceutical talc was first discussed in the medical and scientific literature beginning in the 1940s.^{15–17} Asbestos contamination of talc products is understood to occur during the mining process, in which talc deposits overlap or lie in close proximity to naturally occurring asbestos deposits.^{18–22} The natural presence of asbestos within talc deposits makes selective mining or the extrication of asbestos from mined talc nearly impossible.¹⁹ During application in its commercial talcum powder form, asbestos fibers become airborne and can be inhaled.^{23,24} In 1968, Cralley et al²⁵ found the

presence of three different types of asbestos fibers in 22 of 22 talcum products tested (tremolite, anthophyllite, and chrysotile). However, talcum powder is still widely produced and consumed with a reported 58.3 million adults using body and baby powder in the United States in 2017.²⁶

While the relationship between occupational exposure to asbestos and mesothelioma is well established, multiple studies have shown that not all individuals who develop mesothelioma can pinpoint exposures to asbestos.^{8,11} Among women, occupational exposure explains less than half of malignant mesothelioma cases.^{27,28} Some studies have focused on conventional exposure categories that for women only reflect take home exposures from (male) family members who worked in one of the selected occupations. In one such study, data on home or personal use exposures were not collected, yet increased amounts of tremolite asbestos fibers noted in the lungs of women with MM with no identified source of asbestos contact led study authors to hypothesize that the tremolite could be related to talcum powder use.²⁸ The high prevalence of unexplained or, “idiopathic mesothelioma” among women necessitates further inquiry into potential non-occupational exposures, such as exposure to asbestos-contaminated talcum powder.

In light of these gaps in the existing literature, we present 33 cases of individuals with malignant mesothelioma who were exposed to commercial talcum powder products. Of those cases, we present six in detail, where the individuals had no other known exposure to asbestos and for whom tissue studies show the presence of asbestos commonly found in talcum powder (such as tremolite, and/or anthophyllite). For all 33 cases, other potential exposures to asbestos were considered, with no identified source apart from the talcum powder. The cases were referred to author J.M. for medico-legal evaluation as part of tort litigation, and tissue digestions were performed by author R.G. as part of this litigation. In every case, a pathology report confirmed the diagnosis of malignant mesothelioma. This study was conducted with approval from the Northwell Health Feinstein Institute for Medical Research (#18-0225 FIMR).

MATERIALS AND METHODS

Case Histories

Data gathered for all 33 patients were gathered from each individual's medical records and sworn testimony (deposition transcripts) of individuals. All cases were reviewed by an occupational physician with experience evaluating asbestos exposure in thousands of patients. Data abstracted included medical diagnosis, review of pathology reports confirming the diagnosis of malignant mesothelioma, and clinical course. Exposure data was obtained from sworn testimony by the cases, which included extensive questioning regarding all sources of asbestos exposure. This included family occupational histories (parents and anyone cohabitating with the patient) for all cases to assess potential asbestos exposure, hobbies that included use of products that might contain asbestos (such as ceramics), residence in an area that might have had asbestos industry leading to possible environmental exposures, known abatement of asbestos while the patient was in school, home renovations that might have used asbestos containing materials, and any other potential sources of asbestos exposure. Additional data related to family history of cancers was obtained from the sworn testimony. Any data related to potential genetic mutations such as BRCA1 associated protein-1 was collected, if present.

From the Northwell Health Department of Occupational Medicine Epidemiology and Prevention (Dr Moline, Ms Bevilacqua); Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead (Ms Alexandri); Department of Pathology, The Icahn School of Medicine at Mount Sinai (Dr Gordon), New York, New York.

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Conflicts of Interest: Authors J.M. and R.G. have served as expert witnesses in asbestos litigation, including talc litigation for plaintiffs.

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Clinical Significance: This manuscript is the first to describe mesothelioma among talcum powder consumers. Our case study suggest that cosmetic talcum powder use may help explain the high prevalence of idiopathic mesothelioma cases, particularly among women, and stresses the need for improved exposure history elicitation among physicians.

Address correspondence to: Jacqueline Moline, MD, Northwell Health, Great Neck, NY (jmoline@northwell.edu).

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Talcum powder exposure histories were reviewed based on sworn testimony by patients and in some cases, family members with first-hand knowledge of the use of talcum powder, such as parents who recalled using talcum powder while diapering the patient. Data including type of talcum powder used (Appendix 3, <http://links.lww.com/JOM/A651>), age at first use of talcum powder, and duration of use was obtained to ensure adequate latency from first exposure was present.²⁹ In some cases, individuals were also interviewed in person, and these data were merged with the data obtained in medical records and deposition transcripts.

The six cases described below also had tissue digestions performed by author R.G. These case reports are presented in greater detail; their clinical course was similar to all 33 cases evaluated, and the same rigor with respect to obtaining information related to any asbestos exposure was applied to all 33 cases.

Case 1

Case 1 is a 70-year-old woman who presented to a physician with shortness of breath and chest pain in January 2015. A chest x-ray revealed a small pleural effusion with left basilar atelectasis. In August 2015, a CT angiogram showed development of two sub-pleural nodules anterior to the lingula and a pleural based mass; a pleural effusion was still present. A thoracentesis was done and the cytology showed large clusters of cells suspicious for mesothelioma. A positron emission tomography (PET) scan showed pleural thickening and focal intense uptake inferiorly and posteriorly on the left side of her chest. In September 2015, she underwent thoracoscopic surgery. The pathology showed epithelial malignant mesothelioma with invasion of the visceral pleura and pulmonary parenchyma with tumor present at the stapled margin.

Case 1 applied loose face powder on a daily basis from the 1940s to the 1970s. Her mother also used the same loose face powder and Case 1 cleaned residual powder from her mother's dresser and clothing every other week from 1994 to 2012.

Electron microscopic analysis (EMA) of the lung tissue revealed anthophyllite fibers in a calculated concentrations of 3286 fibers per gram weight. There was also significant amount of fibrous and platy talc and aluminum silicates.

Case 1 was treated with four cycles of combination chemotherapy with cisplatin and pemetrexed for four cycles.

Case 2

In August 2015, Case 2, a 65-year-old woman presented with exertional dyspnea and dry cough. A chest x-ray showed a large left pleural effusion. A chest CT scan in September 2015 showed a freely-movable, large-volume, left pleural effusion, nodularity/lobulation of the left pleura, left lower lobe atelectasis, three nodules in the left upper lobe, and no hilar or mediastinal lymphadenopathy. A thoracentesis showed carcinoma cells. A PET-CT scan on September 22, 2016 reported showed abnormal deposits of tumor in the left pleura. There was no reported disease outside the chest.

Case 2 underwent a bronchoscopy in October, 2015. Pathology showed malignant mesothelioma, biphasic mixed type (50% sarcomatoid, 50% epithelioid). A second opinion confirmed the diagnosis. She underwent two cycles of chemotherapy with doxorubicin, ifosfide, and mensa and completed treatment in November. A PET scan showed no response to the chemotherapy. In December, Case 2 underwent left radical pleurectomy/decortication, resection of left hemidiaphragm, and one lymph node dissection. Surgical pathology showed residual biphasic malignant mesothelioma with negative nodes and negative margins. In January 2016, radiation oncology recommended adjuvant radiation therapy to the left chest, which she received in February and March of 2016. As of April 2016, Case 2 had no evidence of disease recurrence.

Case 2 reported starting to use talc around age eight or nine and would apply powder after her daily shower or bath. She would

also use talcum powder when visiting her grandmother because she enjoyed the scent and would apply the powder before going on a date. She continued to use powder after getting married and used baby powder with all three of her children. In the early 2000s she began to regularly apply a fragrance and its matching talcum powder in the morning and at night, describing it as her signature scent. She also sprinkled the powder in her lingerie drawer and traveled with the powder which she would rub on her suitcases and other surfaces.

EMA of the lung tissue revealed anthophyllite fibers in a calculated concentration of 8625 fibers per gram wet weight with a limit of detection of 2875 fibers per gram wet weight. A significant amount of fibrous and platy talc was seen. EMA of the lymph node tissue revealed anthophyllite and tremolite fibers in a calculated concentrations of 34,500 fibers per gram wet weight with a limit of detection of 11,500 fibers per gram wet weight. They were seen in a ratio of 2:1 anthophyllite:tremolite/actinolite. All fibers counted were 5 μ m or greater in length with aspect ratios greater than 8. There was also some amount of fibrous and platy talc noted in the lymph node tissue.

Case 3

In September 2014, Case 3, an 84-year-old woman, developed shortness of breath, a cough, and chest tightness. A chest x-ray in November 2014 showed a large left pleural effusion. A CT angiogram showed a large left pleural effusion with compressive atelectasis of the left middle and lower lobes and ground glass opacities in the left upper lobe and right lung. A thoracentesis showed carcinoma cells. Case 3 underwent a video thoracoscopy with pleural biopsy and evacuation of a pleural effusion. Pathology revealed a malignant epithelial neoplasm consistent with malignant epithelial mesothelioma. Case 3 then underwent a left pleurectomy and decortication in June 2015. The mesothelioma had spread to the lymph nodes and chest wall, and the pathology now showed malignant biphasic mesothelioma. Case 3 entered hospice care in September 2015 and died in late October 2015.

Case 3 worked as an elementary school teacher with no known occupational exposure to asbestos. Case 3 used talcum powder "before [she] was 12 and 13 years old," applying it under her arms and in her shoes daily. She shook the powder out of the can and applied it onto her body. She noted that her mother also used talcum body powder, and they shared a small bathroom. She used talcum powder beginning in the 1940s and continuing for decades, until her preferred brand was no longer available for purchase.

EMA of the lung tissue did not reveal any asbestos fibers above the limit of detection of 6900. However, there were a number of very small chrysotile asbestos fibers. Analysis of the lymph node tissue revealed tremolite asbestos fibers in calculated concentrations of 9409 fibers per gram wet weight with a limit of detection of 9409. All fibers counted were 5 μ m or greater in length with aspect ratios greater than 20. There was also a significant amount of aluminum silicates, silica particles, and both fibrous and platy talc. Light microscopic analysis revealed a calculated concentration of 409 asbestos bodies per gram wet weight of lymph node tissue by phase contrast light microscopy.

Case 4

In August 2014, Case 4, a 66-year-old woman, developed abdominal pain and had a CT scan of the abdomen and pelvis that showed omental caking, ascites, a fluid pocket in the right lower quadrant, and enlarged diaphragmatic lymph nodes. She underwent a paracentesis and an omental biopsy in August 2014. The cytology revealed atypical mesothelial cells. She then underwent a laparotomy, appendectomy, omentectomy, and left salpingo-oophorectomy. The pathology showed malignant epithelioid mesothelioma. In September 2014, a PET/CT showed increased uptake in the abdomen consistent with malignant ascites, omental metastatic disease, and cardiophrenic

nodules. A thoracoscopy showed tumor covering the right hemidiaphragm. She was treated with multiple rounds of chemotherapy with cisplatin and pemetrexed and therapeutic paracenteses due to persistent ascites. Her tumor progressed, and she died in February 2016. She was 68 years old.

Case 4 grew up in a home where her mother used talcum powder “for as long as [she could] remember.” She recalled personally using talcum powder starting around the age of 9 or 10, applying the powder to her armpits, groin, and around her body, using a powder puff. She applied talcum powder to her body for approximately 40 years. Case 4 had additional exposure to talcum powder in the 1960s while working as a licensed cosmetologist, applying talcum powder on clients’ necks after a haircut. She shook the talcum powder onto the client’s neck, and would wipe off the excess with a brush or blow dryer. She also used talcum powder inside the gloves that she donned prior to applying hair color.

EMA of the peritoneal tissue revealed chrysotile type asbestos fibers in a calculated concentration of 920 fibers per gram wet weight with a limit of detection of 920 fibers per gram wet weight. Fibrous and platy talc was also observed. Also seen were non-asbestiform tremolite and silica crystals.

Case 5

Case 5 was a 76-year-old woman who developed chest pain and fatigue in September 2015 and was diagnosed with viral pericarditis. A CT scan in October 2015 showed mild pericardial thickening and mild perihepatic ascites. She was treated with steroids for viral pericarditis. In late fall 2015, Case 5 developed decreased appetite, weight loss, tenderness around the umbilicus, and abdominal pain. In December 2015 she had an abdominal ultrasound that showed a mild to moderate amount of ascites. An abdominal CT scan showed slightly bilateral pleural thickening with minimal linear atelectatic change. There was copious perihepatic ascites extending to the right and left paracolic gutter and deep pelvis, nodularity at the paracolic gutter, and a right sided deep pelvic mass. A paracentesis was done and showed atypical epithelioid cells and tissue fragments with an inflammatory background. A laparoscopy showed peritoneal carcinomatosis with a diffuse miliary excrescence, a moderate sized pelvic mass and ascites. In January 2016 she underwent an exploratory laparotomy and resection of the omentum, spleen, resection of abdominal tumor, and resection of the abdominal wall tumor. The pathology showed malignant mesothelioma involving the omentum, spleen, colon, and mesentery, as well as the fibroadipose tissue of the peritoneum. Malignant mesothelioma also involved the parietal peritoneum as well as the appendix, with fibrous obliteration of the appendiceal lumen. Case 5 died in October 2017.

Case 5 had daily personal use of talcum body powder from the 1950s to the mid-1970s. She would pour the powder onto her hands and pat it under her arms, in her genital area, between her toes, and on her legs. When she was menstruating she would apply talcum powder on her feminine napkins and her underwear. She also applied talcum powder to her shoes. Case 5’s husband also used talcum powder. Both Case 5 and her husband applied the powder in the bathroom. She shook the bathroom floor mat and cleaned up residual powder from the bathroom sink.

EMA of the omental tissue did not reveal any asbestos fibers above the limit of detection of detection of 651 fibers per gram wet weight. EMA of the lymph node tissue revealed chrysotile and anthophyllite asbestos fibers in a calculated concentrations of 20,700 fibers per gram wet weight with a limit of detection of 10,350 fibers per gram wet weight. All fibers counted were 5 μ m or greater in length with aspect ratios greater than 20. There was also a significant amount of fibrous and platy talc as well as fibrous and platy aluminum silicates.

Case 6

Case 6 is a 44-year-old man who developed chest pain after playing hockey in 2012 and was evaluated in the Emergency Department. A CT scan that showed no pulmonary abnormalities. Case 6 continued to have chest pain over the next 4 years and underwent multiple cardiac evaluations. A CT scan in February 2016 showed increased pleural thickening or non-calcified pleural plaque along the right major fissure and anterior right hemithorax along the right upper lobe. A PET/CT scan in March 2016 showed unilateral hypermetabolic pleural fissural and non-fissural soft tissue abnormalities suspicious for malignancies involving the pleura. There were non-specific tiny parenchymal lung nodules. Case 6 underwent a tissue biopsy in March 2016. The pathology showed malignant epithelioid mesothelioma with invasion to the skeletal muscle.

Case 6 underwent neo-adjuvant chemotherapy with pemetrexed, cisplatin, and bevacizumab in April 2016. In May 2016, Case 6 underwent a mediastinoscopy which showed metastatic spread to the level VII lymph node. Additional chemotherapy was administered, which was not well tolerated. In July 2016, a parietal pleurectomy was done along the fissure between the upper and lower lobe. There was spread to the site of previous inferior right chest tube site. Case 6 developed acute thrombus in the right upper extremity. In September 2016, a chest x-ray showed unchanged right pleural thickening versus a small right pleural effusion. Three additional cycles of chemotherapy were recommended. A PET/CT scan in November 2017 showed a persistent hypermetabolic focus in the right anterobasal pleura and a slight increase in a right pleural effusion.

Case 6 was exposed to talcum powder beginning when he was an infant. His mother applied it to him after his bath until he was able to apply it himself, starting around the age of six. Case 6 recalled using the powder in the bathroom and in his room, and that there would be powder on his floor. He applied the talcum powder directly to his torso, groin, legs, and back, often twice a day after showering. He played hockey as a youth and used powder in his hockey gear before donning the equipment. He recalled getting mouthfuls of powder during the application. He often applied talcum powder once or twice a day after showering. He had no occupational exposure to asbestos.

EMA of the lymph node tissue revealed anthophyllite and tremolite asbestos fibers in a calculated concentrations of 17,250 fibers per gram wet weight with a limit of detection of 3450 fibers per gram wet weight. They were seen in a ratio of 2:3 anthophyllite:tremolite. All fibers counted were 5 μ m or greater in length with aspect ratios greater than 14.7 or greater. There was also some amount of fibrous and platy talc along with platy aluminum silicates and magnesium aluminum silicates.

Tissue Sample Analysis

Tissue samples from six patients were analyzed: (a) lung and lymph node tissue from four of the patients diagnosed with pleural mesothelioma; and (b) lung and lymph node from two of the patients diagnosed with peritoneal mesothelioma. The tissue samples had been preserved in paraffin blocks or as formalin fixed tissues.

Tissue Digestion Protocols

Paraffin Blocks

The tissue was extracted from paraffin blocks was done according to the methodology described in Heller et al³⁰ and Wu et al.³¹ The tissues were cut from the paraffin blocks and deparaffinized by melting and xylene treatment. They were brought to water, blotted and weighted. The tissues were digested with KOH and the inorganic pellet cleaned with distilled water by multiple centrifugation steps on an asbestos locator grid coated with formvar. In

addition, 250 μ L samples were prepared using a cytocentrifuge onto a standard glass slide to identify ferruginous bodies and longer fibers by phase contrast microscopy.

Formalin Fixed Tissue

This protocol is similar to above without the deparaffinizing step as described in^{23,39}. Controls for both the paraffin and formalin fixed tissues included looking at the paraffin, if from blocks, the formalin, if from fixed wet tissue, or any other materials used to process the tissue to view the remaining inorganic material on the grids.

Asbestos Fiber Counting

The grids were analyzed two ways: (a) transmission electron microscopy (TEM) using a standard fiber-counting protocol (23,40)^{23,32} on 800 grid openings; and (b) phase contrast light microscopy on two cytocentrifuge preparations per tissue type in accordance with a standard asbestos body-counting protocol (23,40).^{23,32} Asbestos fibers were evaluated to determine whether they met the definition of a fiber, which includes having at a 5:1 length:width ratio and parallel sides and at least 5 μ m in length. The fibers were also analyzed by Energy Dispersive Spectroscopy (EDS) to determine the ratio of elements contained in the fibers and by Selected Area Electron Diffraction (SAED) to confirm the crystalline structure of the fiber to confirm that they were asbestos. To evaluate for potential contamination, control samples were prepared from the same distilled water used to wash the samples and the paraffin surrounding the tissue. Verification techniques of fiber counting were used for quality control and quality assurance. All fibers, regardless of size, were counted in 800 grid openings.

Calculating Asbestos Fiber Concentration

TEM and PCM

Asbestos fiber concentration in the samples examined with transmission electron microscopy was calculated (see Appendix 1, <http://links.lww.com/JOM/A649>). The 250 μ L samples centrifuged onto standard microscope slides were examined using phase contrast light microscopy (Appendix 2, <http://links.lww.com/JOM/A650>). The asbestos fiber concentration in these samples was calculated (see Appendix 2, <http://links.lww.com/JOM/A650>).

Control Samples

Background control samples were obtained at autopsy or from surgical specimens from pulmonary or obstetrical and gynecologic pathologists. Samples included lung, thoracic, mesenteric and abdominal lymph nodes, abdominal tissue, ovaries, fallopian tubes, uteri and mesentery tissue. Exposure histories had been obtained by treating pulmonologists or surgeons from all individuals; all were screened for asbestos exposure from personal use, family exposure, and personal or family use of talcum powder. For those patients in whom there was any question of asbestos exposure from any source, the pathologists conferred with the treating clinician to ensure there was no known asbestos exposure. If there was potential asbestos exposure, the specimens were not included in the group. As a result, the background control specimens reflect only asbestos exposure from the overall community.

RESULTS

The data associated with the exposure history of all 33 patients is presented in Table 1. The table identifies talcum powder as the only asbestos exposure these patients have experienced. No individual identified any asbestos exposure apart from contaminated talcum powder from workplace or household exposures.

Table 2 provides the results of the fiber burden analyses for the six cases in which asbestos fibers were identified in the anatomic vicinity of the patients' mesotheliomas. Uniformly, the tissue fiber burdens reveal the presence of the following: talc, aluminum silicates, aluminum magnesium silicates, silica crystals, and asbestos fibers. The asbestos fibers are all anthophyllite, tremolite, and/or chrysotile. These three types are typical contaminants of talcum powders.¹⁹ They have been identified as contaminants in talcum powders in repeated laboratory testing at numerous institutions.^{33–37} The tissue fiber burdens contained no amosite or crocidolite, commercial amphibole asbestos fibers. Testing results of talcum powders have failed to show the presence of commercial amphiboles.

Table 3 presents the asbestos fiber burden results from background controls in tissues from autopsy and surgical population with no evidence of ovarian cancer or other malignancy, and with no known asbestos exposure. The lung and lymph nodes sampled showed only chrysotile and non-commercial amphibole asbestos in a small percentage of control samples—six of the 35 control samples, or 17%. All women with asbestos present were over 60 years of age. While asbestos is present at extremely low concentrations in the ambient air,³⁸ in the control samples presented in the study, there was no evidence of asbestos in women under the age of 60 years of age. Two fibers were seen in two specimens and one fiber was seen in four samples, all under 1 μ m in size. The asbestos fiber burdens in the six talc exposed patients were all greater than the control population. No aluminum silicates, aluminum magnesium silicates, and silica crystals, all components of talcum powder identified in our patients, were not found in the control population that did not use talcum powder.

DISCUSSION

This paper provides the first large case series to identify cosmetic talcum powder contaminated with asbestos as the cause of malignant mesothelioma in cosmetic talc users. In 1960, Wagner presented 33 individuals exposed to crocidolite asbestos from occupational and environmental exposures, providing the first large case series of individuals diagnosed with mesothelioma with clearly identifiable exposure to asbestos.² Since then, the high prevalence of idiopathic mesothelioma cases suggested other possible exposures, including exposure to asbestos contaminated talc. Like Wagner, we present 33 cases, predominantly of women, who had no known exposure to asbestos other than prolonged use of talcum powder. This is consistent with the distribution of talcum powder usage in the United States, with greater numbers of women using powder than men.²⁶ Furthermore, the six case histories detailed years or decades of talcum powder use as well as tissue analysis that showed asbestos present in either tumor tissue or lymph nodes. In all six cases, asbestos fibers consistent with those identified as contaminants in repeated laboratory testing of talcum powder samples across several institutions were identified.^{20,23,33,39} Notably, the fiber types found were consistent with the types of asbestos found in talc. Amosite and crocidolite, asbestos fibers that are encountered in cases of industrial and occupational exposure, not cosmetic talcum powder,⁴⁰ were not found in any of these cases.

This paper is also the first, to the authors' knowledge, to utilize background controls for which an extensive exposure history was elicited and for which no known asbestos exposure had occurred. Background controls are the best comparison when analyzing tissue of asbestos exposed individuals however, one of the biggest challenges is to choose a population of patients with no history of environmental or occupational exposure to asbestos apart from ambient air concentration of asbestos. Previous fiber burden studies of non-occupationally exposed individuals have compared the asbestos content in their tissue to workers in the same community where asbestos mines or asbestos containing factories were

TABLE 1. Description of 33 Mesothelioma Cases

Talcum Powder Exposure								
Case	Sex	Year of Diagnosis	Age at Diagnosis	Mesothelioma Site	Histology	Talcum Powder Brand	Estimated Years of Use	Occupation (s)
1*	F	2015	70 [†]	Pleural	Epithelial	A	30	Medical technician
2*	F	2015	65	Pleural	Biphasic	C, H, V	50	Homemaker
3*	F	2014	82 [†]	Pleural	Biphasic	C	70	Teacher
4*	F	2014	66 [†]	Peritoneal	Epithelial	B, C	30	Hairdresser
5*	F	2015	75 [†]	Peritoneal	Epithelial	C	25	Teacher
6*	M	2016	43	Pleural	Epithelial	D	40	Finance
7	M	2016	65	Peritoneal	Epithelial	D	62	None provided
8	M	2016	76 [†]	Pleural	Epithelial	U	38	Accountant
9	F	2016	66 [†]	Pleural	Epithelial	C, E	35	Hair dresser
10	F	2015	80	Pleural	Epithelial	F	30	Administrative assistant
11	F	2018	73	Pleural	Epithelial	C, V	30	Flight attendant
12	F	2017	57	Peritoneal	Epithelial	A, D, G, H, I	40	Medical technologist
13	M	2016	56	Peritoneal	Biphasic	D, I, S	15	Maintenance worker
14	M	2017	56	Peritoneal	Epithelial	D	50	Molding press operator
15	F	2016	40	Peritoneal	Epithelial	D, J	12	Retail worker
16	F	2015	30	Pleural	Epithelial	D, K, L, M	19	Retail worker
17	F	2015	80 [†]	Pleural	Epithelial	A, C, N	40	Office worker
18	F	2015	64	Pleural	Sarcomatoid	C	40	Real Estate agent
19	F	2009	62	Pleural	Epithelial	C	15	Teacher and fitness instructor
20	F	2016	69	Peritoneal	Epithelial	D, G	30	Hair dresser
21	F	2013	34 [†]	Peritoneal	Epithelial	C	10	Teacher
22	F	2018	59	Pleural	Epithelial	C, D	42	School custodian
23	F	2016	27	Peritoneal	Epithelial	D, O	10	Not provided
24	F	2016	38	Peritoneal	Epithelial	D, I	18	Social services
25	F	2017	64	Pleural	Epithelial	D, G, J	27	Mathematician
26	F	2016	83	Pleural	Epithelial	C, D, I	60	Not provided
27	F	2017	41	Peritoneal	Epithelial	D	30	Computer programmer
28	F	2016	79	Peritoneal	Epithelial	A, C, T,	21	Not provided
29	M	2015	46	Pleural	Epithelial	D, R, U	15	Informational technology
30	F	2016	88 [†]	Pleural	Epithelial	A, D, C, I	80	Administrative worker
31	F	2017	53	Pleural	Epithelial	D	23	Cleaner
32	F	2017	76	Pleural	Epithelial	D, C	17	Rehabilitation coordinator
33	F	2017	46	Peritoneal	Epithelial	D	25	Clerical worker

*Tissue analysis presented done by author. Tissue analysis might have been done in some cases by other investigator, these results are not presented in this paper.

[†]Deceased as of writing; vital status of many individuals is currently unknown.

present.^{41,42} Autopsy studies have been performed^{43–45} in individuals without a specific history of workplace asbestos exposure; full exposure histories were not obtained. Langer measured asbestos fiber burdens in New York City residents with no known history of asbestos.⁴⁶ Roggli and Longo⁴⁷ measured tissue burdens for individuals who had bystander or household exposure from family members who directly worked with asbestos in their work, such as laundering clothes. However that type of exposure does not truly reflect background or “unexposed” individuals. Lee and Van Orden³² measured background air exposure in and outside of buildings. They found short chrysotile, tremolite, and actinolite fibers, but no anthophyllite or crocidolite, and very small levels of

amosite. Lee and Van Orden’s results are consistent with the background asbestos fibers found in the older women the present study.³² While fiber burden studies are rarely undertaken in the course of clinical treatment, and are used primarily for medico-legal purposes, the findings of various fibers in the lung tissues can provide guidance as to potential prior asbestos exposure, whether from occupation, residential, or para-occupational exposure to asbestos. Attention to true background rates for fiber burdens is critical.⁴⁸

Our findings strongly suggest that asbestos exposure through asbestos-contaminated cosmetic talc explains cases once deemed idiopathic or “spontaneous,” and underline the importance of

TABLE 2. Tissue Digestion of Six Mesothelioma Cases

Case	Sex	Mesothelioma Site	Asbestos Type	Site Found	Concentration (Fibers/g) (Lung, Lymph)	Limit of Detection (Lung, Lymph)	Asbestos Bodies
1	F	Pleural	Anthophyllite	Lung	3,286	1,643	0
2	F	Pleural	Anthophyllite, tremolite, actinolite	Lung, lymph node	8,625, 34,500	2,875, 11,500	0
3	F	Pleural	Tremolite	Lung, lymph node	0, 9,409	6,900, 9,409	0, 409
4	F	Peritoneal	Chrysotile	Peritoneum	920	920	0
5	F	Peritoneal	Anthophyllite	Lymph node	20,700	10,350	0, 0
6	M	Pleural	Anthophyllite, tremolite	Lymph node	17,250	3,450	0

TABLE 3. Current Levels of Asbestos Fiber Burden Observed in Digests of Tissue From Autopsy and Surgical Population With no History of Asbestos Exposure (Controls)

Tissue Type	N	Asbestos Type	Mean (Fibers/Gram Wet Weight)*	Range (Fibers/Gram Wet Weight)
Lung tissue	35	Chrysotile	892	0–30,000
		Tremolite	84	0–1,552
		Chrysotile and tremolite	35	0–1,208
		Asbestos bodies	<1 bodies/gram wet weight	0–6
Paratracheal or parachronchial lymph node tissue	35	Chrysotile	72	0–1,1035
		Tremolite	29	0–552
		Chrysotile and tremolite	24	0–828
		Asbestos bodies	<1 bodies/gram wet weight	0–5
Peritoneum + gynecological tissue	10	Chrysotile	0	0
		Tremolite	0	0
		Chrysotile and tremolite	0	0
		Asbestos bodies	0	0

*All fibers that were counted were always 1 μ m or less in length.

collecting detailed exposure histories that incorporate these findings in patients presenting with mesothelioma. Several factors may hinder the collection of comprehensive exposure histories among individuals diagnosed with mesothelioma. Minimal training in occupational medicine and exposure taking practice among medical students may contribute to a lack of or incomplete exposure history elicitation on the part of clinicians.^{49,50} Secondly, long latency periods between exposure and illness pose a challenge both to individual recall as well the ability to establishing causality. Due to the relatively short period between diagnosis and death among mesothelioma patients, patients are often too ill or are deceased before being able to provide a full history. Furthermore, though the presence of asbestos in talc and talcum powder was first discussed in the scientific literature in the 1940s, individuals may not be aware that the products they used contained asbestos. Few clinicians are aware that this is a potential exposure. Typically, patients with mesothelioma will be simply asked whether they worked with or around asbestos, rather than being providing with a listing of potential sources of the types of exposure in which one might encounter asbestos. Cases of mesothelioma among hairdressers characterized as idiopathic also underscore the contribution of an incomplete exposure history; the potential failure to identify the use of talcum powder exposure in their work would prevent the linking of occupational exposure to asbestos to their mesothelioma. In our paper, there were three female hairdressers who regularly used talcum powder in their work. It was unclear from any of the histories noted in the medical records that these women were asked if they used talcum powder as part of the hair cutting process. In a report from the National Mesothelioma Registry of Italy, staff noted a cluster of mesothelioma due to “unknown exposure” among hairdressers, but only examined hairdryer use as a potential exposure. There was no discussion of the occupational use of talcum powder.⁵¹ However, McDonald et al,⁵² noted that a barber’s occupational exposure to asbestos to talc could explain the increased finding of tremolite in the individual’s lung fiber burden.

The case series presented should be understood in the context of its limitations. Data were obtained from medication records and transcripts of depositions, rather than structured, in-person interviews. However, the information solicited during the course of the patients’ depositions were thorough, and included exhaustive questioning about alternative sources of asbestos exposure, including household exposure, exposures from external industrial sources, occupational exposure, and potential exposure from family members. While deposition testimony is by definition self-report,

depositions were given under oath and the potential for recall bias noted would be presented whether patients completed a structured interview or were asked questions during sworn testimony. Furthermore, the utilization of medical records allowed the authors to corroborate important medical information and confirm the pathological diagnosis.

In March 2019 the Federal Drug Administration (FDA) released a statement as an update to their 2017 finding, confirming asbestos contamination of certain cosmetic products marketed and sold to young girls and outlining new steps to work with manufacturers to ensure the safety of their products.⁵³ While such public acknowledgment of the potential for asbestos contamination in cosmetic talc marks an important turning point, manufacturers are not legally obligated to register cosmetic products with the FDA. The results of this study coupled with the widespread use of such products²⁶ underline the continued risks posed to consumers through common household and cosmetic products. While these products remain unregulated and on the shelves, the use of talcum powder must be incorporated into standard exposure history practice in order to promote earlier detection of asbestos related disease among non-occupationally exposed individuals. This paper provides evidence that mesothelioma cases once considered idiopathic may be attributable to asbestos-contaminated cosmetic talcum powder usage and that the elicitation of a history of such usage is imperative to obtaining a full exposure history in all patients presenting with mesothelioma.

REFERENCES

1. Straif K, Benbrahim-Tallaa L, Baan R, et al. A review of human carcinogens—Part C: metals, arsenic, dusts, and fibres. *Lancet Oncol*. 2009;10:453–454.
2. Wagner JC, Sleggs CA, Marchand P. Diffuse pleural mesothelioma and asbestos exposure in the North Western Cape Province. *Occup Environ Med*. 1960;17:260–271.
3. Britton M. The epidemiology of mesothelioma. *Semin Oncol*. 2002;29:18–25.
4. Iwatsubo Y, Pairon JC, Boutin C, et al. Pleural mesothelioma: dose-response relation at low levels of asbestos exposure in a French population-based case-control study. *Am J Epidemiol*. 1998;148:133–142.
5. Agudo A, González CA, Bleda MJ, et al. Occupation and risk of malignant pleural mesothelioma: a case-control study in Spain. *Am J Ind Med*. 2000;37:159–168.
6. Magnani C, Agudo A, González CA, et al. Multicentric study on malignant pleural mesothelioma and non-occupational exposure to asbestos. *Br J Cancer*. 2000;83:104.
7. Rödelberger K, Jöckel K-H, Pohlabein H, Römer W, Weitowitz H-J. Asbestos and man-made vitreous fibers as risk factors for diffuse malignant mesothelioma: Results from a German hospital-based case-control study. *Am J Ind Med*. 2001;39:262–275.

8. Lacourt A, Gramond C, Rolland P, et al. Occupational and non-occupational attributable risk of asbestos exposure for malignant pleural mesothelioma. *Thorax*. 2014;69:532–539.
9. Markowitz S. Asbestos-related lung cancer and malignant mesothelioma of the pleura: selected current issues. *Semin Respir Crit Care Med*. 2015;36:334–346.
10. Doll R. Mortality from lung cancer in asbestos workers. *Br J Ind Med*. 1955;12:81–86.
11. Marinaccio A, Corfiati M, Binazzi A, et al. The epidemiology of malignant mesothelioma in women: gender differences and modalities of asbestos exposure. *Occup Environ Med*. 2017;75:254–262.
12. Lemen RA. Mesothelioma from asbestos exposures: epidemiologic patterns and impact in the United States. *J Toxicol Environ Health Part B*. 2016;19:250–265.
13. Henley SJ, Larson TC, Wu M, et al. Mesothelioma incidence in 50 states and the District of Columbia, United States, 2003–2008. *Int J Occup Environ Health*. 2013;19:1–10.
14. Mazurek JM. Malignant mesothelioma mortality—United States, 1999–2015. *MMWR Morb Mortal Wkly Rep*. 2017;66:214–218.
15. Porro F, Patton J, Hobbs A. Pneumoconiosis in the talc industry. *Am J Roentgenol*. 1942;47:507.
16. Hopkins O. A report on the asbestos, talc, and soapstone deposits of Georgia; 1948.
17. van Horn E. Talc deposits of the Murphy marble belt; 1948.
18. Paoletti L, Caiazza S, Donelli G, Pocchiari F. Evaluation by electron microscopy techniques of asbestos contamination in industrial, cosmetic, and pharmaceutical talcs. *Regul Toxicol Pharmacol*. 1984;4:222–235.
19. Rohl AN, Langer AM. Identification and quantitation of asbestos in talc. *Environ Health Perspect*. 1974;9:95–109.
20. Rohl AN, Langer AM, Selikoff IJ, et al. Consumer talcums and powders: mineral and chemical characterization. *J Toxicol Environ Health*. 1976;2:255–284.
21. Kleinfeld M, Messite J, Langer AM. A study of workers exposed to asbestiform minerals in commercial talc manufacture. *Environ Res*. 1973;6:132–143.
22. Luckewicz W. Differential thermal analysis of chrysotile asbestos in pure talc and talc containing other minerals. *J Soc Cosmet Chem*. 1975;26:431–437.
23. Gordon RE, Fitzgerald S, Millette J. Asbestos in commercial cosmetic talcum powder as a cause of mesothelioma in women. *Int J Occup Environ Health*. 2014;20:318–332.
24. Longo DL, Young RC. Cosmetic talc and ovarian cancer. *Lancet*. 1979;314:349–351.
25. Cralley LJ, Key MM, Groth DH, Lainhart WS, Ligo RM. Fibrous and mineral content of cosmetic talcum products. *Am Ind Hyg Assoc J*. 1968;29:350–354.
26. Simmons. U.S. Brands of body and baby powder used 2017 | Statista. Available at: <https://www.statista.com/statistics/275421/us-households-brands-of-body-and-baby-powder-used/>. Accessed February 21, 2018.
27. Camiade E, Gramond C, Jutand M-A, et al. Characterization of a French series of female cases of mesothelioma. *Am J Ind Med*. 2013;56:1307–1316.
28. Panou V, Vyberg M, Meristoudis C, et al. Malignant mesothelioma in 91 danish women: the environmental asbestos exposure. *J Clin Oncol*. 2017;35:8560–18560.
29. Lanphear BP, Buncher CR. Latent period for malignant mesothelioma of occupational origin. *JOM*. 1992;34:718–721.
30. Heller DS, Gordon RE, Westhoff C, Gerber S. Asbestos exposure and ovarian fiber burden. *Am J Ind Med*. 1996;29:435–439.
31. Wu M, Gordon R, Herbert R. Lung disease in World Trade Center responders exposed to dust and smoke-carbon nanotubes found in the lungs of WTC patients and dust samples. *Environ Health Perspect*. 2010;118:499–504.
32. Lee RJ, Van Orden DR. Airborne asbestos in buildings. *Regul Toxicol Pharmacol*. 2008;50:218–225.
33. Blount AM. Amphibole content of cosmetic and pharmaceutical talcs. *Environ Health Perspect*. 1991;94:225–230.
34. Snider D, Pfeiffer D, Mancuso J. Asbestos form impurities in commercial talcum powders. *Compass Sigma Gamma Epsil*. 1972;49:65–67.
35. Longo W, Rigler M. Supplemental Expert Report & Analysis of Johnson & Johnson Baby Powder and Valeant Shower to Shower Talc Products for Amphibole Asbestos; 2018.
36. Compton S. Investigation of Italian Talc Samples for Asbestos; 2017.
37. Longo W. Analysis of Johnson & Johnson's Historical Baby Powder & Shower to Shower Products from the 1960's to the Early 1990's for Amphibole Asbestos; 2018.
38. Abelmann A, Glynn ME, Pierce JS, Scott PK, Serrano S, Paustenbach DJ. Historical ambient airborne asbestos concentrations in the United States—an analysis of published and unpublished literature (1960s–2000s). *Inhal Toxicol*. 2015;27:754–766.
39. Investigation of Possible Asbestos Contamination in Talc Samples; 1972.
40. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Carbon Black, Titanium Dioxide, and Talc. Lyon, France: World Health Organization International Agency for Research on Cancer; 2010.
41. Dodson RF, Huang J, Bruce JR. Asbestos content in the lymph nodes of nonoccupationally exposed individuals. *Am J Ind Med*. 2000;37:169–174.
42. Dodson RF, Williams MG, Huang J, Bruce JR. Tissue burden of asbestos in nonoccupationally exposed individuals from east Texas. *Am J Ind Med*. 1999;35:281–286.
43. Churg A. Asbestos fibers and pleural plaques in a general autopsy population. *Am J Pathol*. 1982;109:88–96.
44. Warnock ML, Churg AM. Asbestos bodies. *Chest*. 1980;77:129–130.
45. Srebro SH, Roggli VL, Samsa GP. Malignant mesothelioma associated with low pulmonary tissue asbestos burdens: a light and scanning electron microscopic analysis of 18 cases. *Mod Pathol*. 1995;8:614–621.
46. Langer AM, Selikoff IJ, Sastre A. Chrysotile asbestos in the lungs of persons in New York City. *Arch Environ Health*. 1971;22:348–361.
47. Roggli VL, Longo WE. Mineral fiber content of lung tissue in patients with environmental exposures: household contacts vs. building occupants. *Ann N Y Acad Sci*. 1991;643:511–518.
48. Gordon RE. Analytic Analyses of Human Tissues for the Presence of Asbestos and Talc. In: *Electron Microscopy—Novel Microscopy Trends*. IntechOpen; 2019.
49. Papali A, Hines SE. Evaluation of the patient with an exposure-related disease: the occupational and environmental history. *Curr Opin Pulm Med*. 2015;21:155–162.
50. Politi BJ, Arena VC, Schwerha J, Sussman N. Occupational medical history taking: how are today's physicians doing? A cross-sectional investigation of the frequency of occupational history taking by physicians in a major US teaching center. *J Occup Environ Med*. 2004;46:550–555.
51. Carugno M, Mensi C, Sieno C, Consonni D, Riboldi L. Asbestos exposure among hairdressers. *Med Lav*. 2012;103:70–71.
52. McDonald AD, Case BW, Churg A, et al. Mesothelioma in Quebec chrysotile miners and millers: epidemiology and aetiology. *Ann Occup Hyg*. 1997;41:707–719.
53. Gottlieb S, Mayne S. Statement from FDA Commissioner Scott Gottlieb, M.D., and Susan Mayne, Ph.D., Director of the Center for Food Safety and Applied Nutrition, on Tests Confirming a 2017 Finding of Asbestos Contamination in Certain Cosmetic Products and New Steps That FDA Is Pursuing to Improve Cosmetics Safety; 2019. Available at: <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm632736.htm>. Accessed May 30, 2019.